Applicants: James Binley et al.
Serial No.: 10/780,993
Filed: January 18, 2004
Exhibit 1

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING TRANSMITTAL OF COPY OF INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY (CHAPTER I OF THE PATENT COOPERATION TREATY)
(PCT Rule 44bis.1(c))

To:

WHITE, John, P.
Cooper & Dunham LLP
1185 Avenue of the Americas
New York, NY 10036
ETATS-UNIS D'AMERIQUE

Date of mailing (day/month/year)	
01 February 2007 (01.02.2007)	
Applicant's or agent's file reference	IMPORTANT NOTICE
65845-E-PCT/JPW/JW	

International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/US2005/021091	15 June 2005 (15.06.2005)	15 June 2004 (15.06.2004)

Applicant

PROGENICS PHARMACEUTICALS, INC. et al

The International Bureau transmits herewith a copy of the international preliminary report on patentability (Chapter I of the Patent Cooperation Treaty)

IDS Entered on Search: [65845-DPCT-US; 65845-E-PCT-US] 5/1/07

Applicants: James Binley et al.
Serial No.: 10/780,993
Filed: February 18, 2004
Exhibit 1

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

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Authorized officer

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference 65845-E PCT/JPW/JW	**FOR FURTHER ACTION** See item 4 below	
International application No. PCT/US2005/021091	International filing date (*day/month/year*) 15 June 2005 (15.06.2005)	Priority date (*day/month/year*) 15 June 2004 (15.06.2004)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant PROGENICS PHARMACEUTICALS, INC.		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis*.2).

	Date of issuance of this report 23 January 2007 (23.01.2007)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 82 70	Authorized officer Athina Nickitas-Etienne e-mail: pt04@wipo.int

Form PCT/IB/373 (January 2004)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
JOHN P. WHITE
COOPER & DUNHAM LLP
1185 AVENUE OF THE AMERICAS
NEW YORK, NY 10036

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing (*day/month/year*)	27 DEC 2006
Applicant's or agent's file reference: 65845-E-PCT/JPW/JW	FOR FURTHER ACTION: See paragraph 2 below

International application No.	International filing date (*day/month/year*)	Priority date (*day/month/year*)
PCT/US05/21091	15 June 2005 (15.06.2005)	15 June 2004 (15.06.2004)

International Patent Classification (IPC) or both national classification and IPC

IPC: A61K 39/21(2007.01)
USPC: 424/208.1

Applicant

PROGENICS PHARMACEUTICALS, INC.

1. This opinion contains indications relating to the following items:

- [X] Box No. I — Basis of the opinion
- [ ] Box No. II — Priority
- [X] Box No. III — Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- [ ] Box No. IV — Lack of unity of invention
- [X] Box No. V — Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- [ ] Box No. VI — Certain documents cited
- [ ] Box No. VII — Certain defects in the international application
- [X] Box No. VIII — Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(*b*) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/ US	Date of completion of this opinion	Authorized officer
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (571) 273-3201	14 November 2006 (14.11.2006)	Louise Humphrey, Ph.D. Telephone No. 571-272-1600

Form PCT/ISA/237 (cover sheet) (April 2005)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US05/21091

Box No. I Basis of this opinion

1. With regard to the language, this opinion has been established on the basis of:

☒ the international application in the language in which it was filed

☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

a. type of material

☐ a sequence listing

☐ table(s) related to the sequence listing

b. format of material

☐ on paper

☐ in electronic form

c. time of filing/furnishing

☐ contained in the international application as filed.

☐ filed together with the international application in electronic form.

☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US05/21091

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos. 31,32,80 and 81

because:

☐ the said international application, or the said claim Nos. _____ relate to the following subject matter which does not require an international search *(specify)*:

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 31,32,80 and 81 are so unclear that no meaningful opinion could be formed *(specify)*:

These claims are improper dependent claims under PCT Rule 6.4(a).

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☒ no international search report has been established for said claims Nos. 31,32,80 and 81

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b).

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-bis of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details.

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US05/21091

Box No. V Reasoned statement under Rule 43 *bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims 1-30,33-79 and 82-105	YES
	Claims NONE	NO
Inventive step (IS)	Claims 30,41,44-48,79,93-97,99-101 and 103-105	YES
	Claims 1-29,33-40,42,43,49-78,82-92,98 and 102	NO
Industrial applicability (IA)	Claims 1-30,33-79 and 82-105	YES
	Claims NONE	NO

2. Citations and explanations:

Please See Continuation Sheet

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US05/21091

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the questions whether the claims are fully supported by the description, are made:

Claims 44-48, 93-97, 99-101, and 103-105 are objected to as lacking clarity under PCT Rule 66.2(a)(v) because of the claims not fully supported by the description. The description does not disclose the claimed invention in a manner sufficiently clear and complete for the claimed invention to be carried out by a person skilled in the art because the prevention or delay and reduction of HIV-1 infection is not routinely practiced and highly unpredictable in the art due to the high frequency of mutation during replication, the heterogeneity of the HIV isolates, subtypes, and clades, and the lack of successful trial results.

International application No.
PCT/US05/21091

Supplemental Box
In case the space in any of the preceding boxes is not sufficient.

V. 2. Citations and Explanations:

Claims 1, 3-25, 28, 29, 32-39, 43 and 98 lack an inventive step under PCT Article 33(3) as being obvious over Lu *et al.* (US2004/0191269) in view of Binley *et al.* (2000, Binley'00).

The instant claims are directed to a method for eliciting an immune response in a subject comprising administering to the subject as part of the a regiment (i) more than one dose of a nucleic acid prime, and (ii) more than one dose of a protein boost composition. Lu *et al.* disclose methods for inducing an immune response using protein compositions as boosts following administration of the DNA compositions encoding HIV gp120, gp140, gp160, and/or gp41. See Abstract and ¶79 on page 7. The DNA prime and protein boost are codon-optimized in one example. See ¶149 on page 16. The composition can be administered in multiple doses over an extended period of time, (e.g., over a period of 2, 3, 4 weeks or more, e.g., several months). See ¶13 on page 2. The protein composition can be administered after the nucleic acid composition, e.g., between 4 and 8 weeks after the nucleic acid composition. See ¶19 on page 2. Suitable doses of nucleic acid compositions for humans can range from 1 ug/kg to 1 mg/kg of total nucleic acid, e.g., from 5 ug/kg-500 mg/kg of total DNA, 10 ug/kg-250 ug/kg of total DNA, or 10 ug/kg-170 ug/kg of total DNA. "Total DNA" and "total nucleic acid" refers to a pool of nucleic acids encoding distinct antigens. For example, a dose of 50 mg of total DNA encoding 5 different Env antigens can have 1 mg of each antigen. DNA vaccines can be administered multiple times, e.g., between two-six times, e.g., three times. In an exemplary method, 100 ug of a DNA composition is administered to a human subject at 0, 4, and 12 weeks (100 ug per administration). See ¶77 on page 7. An exemplary range for an immunogenic amount of protein composition is 5 ug/kg-500 ug/kg, e.g., 10-100 ug/kg of total protein, with adjuvant. An exemplary program of administration of the protein composition includes a first intramuscular boost 8 weeks after the final nucleic acid immunization, followed by a second intramuscular boost with the protein composition 8 weeks after the first boost. See ¶85 on page 8. In one example, each group of New Zealand White rabbits received three DNA immunizations at weeks 1, 5, and 13, and two protein boosts at weeks 21 and 29. Animals received DNA immunization either by a gene gun (GG), IM or by ID injection. Proteins were formulated in QS-21 adjuvant and immunized by IM route. See ¶141 on page 14-15. Increased DNA uptake via intramuscular delivery can also be accomplished by electrotransfer. See ¶72 on page 6. Lu *et al.* specifically disclose kits comprising the nucleic acid and protein compositions included with pharmaceutically acceptable carriers. See ¶87 on page 8. Lu *et al.* further suggest using an adjuvant, QS-21 (see ¶85 on page 7), with protein boost compositions, and unmethylated CpG motifs to improve DNA stability and uptake as well as improve

Supplemental Box
In case the space in any of the preceding boxes is not sufficient.

unmune induction (see ¶72 on page 6). Protein compositions can be encapsulated in poly(DL-lactide-co-glycolide) ("PLG") microspheres. See ¶81 on page 7.
Lu *et al.* do not disclose describe amino acid substitutions, A501C and A605C, that allow a disulfide bond between HIV-1 gp120 and gp41.
Binley'00 describe a recombinant HIV-1 envelope glycoprotein complex stabilized by an intermolecular disulfide bond between the gp120 and gp41 subunits, which is an antigenic mimic of the trimeric virion-associated structure. See abstract.. A variety of double cysteine substitutions were introduced into the gp120 and gp41 moieties of gp140 wildtype (HIV-1 JR-FL). A similar strategy was used to make the corresponding cysteine substitutions in other HIV-1 gp140 proteins. A gp120-gp41 cleavage site mutant of JR-FL gp140 uncleaved form was generated by substitution of the sequence Lys-Arg-Arg-Val-Val-Gln-Arg-Glu-Lys-Arg-Ala-Val (the C terminus of gp120 and the first two residues of gp41) by a hexameric Leu-Arg motif. This eliminates the furin cleavage motif (underlined), as described previously. See Figure 3.
It would have been obvious to one skilled in the art, at the time the invention was made, to modify the method of Lu *et al.* so that the protein boost contains the mutations A501C and T605C, which forms a disulfide bond between HIV-1 gp120 and gp41 in an uncleaved form of HIV-1 gp140, and to increase the number of boosts. One would be motivated to do so to stabilize the uncleaved HIV-1 gp140 or gp120-gp41 trimeric complex and to increase the amount of immune response. There would be a reasonable expectation of success given that the resulting gp140 protein is processed efficiently, producing a properly folded envelope glycoprotein complex, and is immunogenic, as suggested by Binley'00.

Claim 27 lacks an inventive step under PCT Article 33(3) as being obvious over Lu *et al.* (US2004/0191269) in view of Binley *et al.* (2002, Binley'02).

The instant invention is further limited to a cleavage-enhanced HIV-1 gp140. The disclosure of Lu *et al.* has been set forth above. Lu *et al.* do not disclose a cleavage-enhanced HIV-1 gp140, however, Binley'02 describe the mutation of the cleavage site in gp140 to enhance its processing by cellular proteases. When the Env cleavage site (REKR) was mutated in order to see if its use by cellular proteases could be enhanced, several mutants were processed more efficiently than the wild-type protein. The optimal cleavage site sequences were RRRRRR, RRRRKR, and RRRKKR. These mutations did not significantly alter the capacity of the Env protein to mediate fusion, so they have not radically perturbed Env structure. See abstract.
It would have been obvious to one skilled in the art, at the time the invention was made, to modify the method of Lu *et al.* so that the protein boost contains a cleavage-enhanced gp140 because uncleaved gp140 and gp160 proteins do not fully mimic the structure of the native trimeric Env complex. As a result, antibodies elicited to gp120 and uncleaved Env proteins can sometimes neutralize the homologous HIV-1 isolate but generally do not cross-neutralize heterologous primary isolates. One would be motivated to do so to increase the immunogenicity of the protein boost. There would be a reasonable expectation of success given that these mutations did not significantly alter the capacity of the Env protein to mediate fusion, so they have not radically perturbed Env structure. Furthermore, unlike that of wild-type Env, expression of the cleavage site mutants was not significantly reduced by furin coexpression. Coexpression of Env cleavage site mutants and furin is therefore a useful method for obtaining high-level expression of processed Env, as suggested by Binley'00.

Claims 2 and 26 lack an inventive step under PCT Article 33(3) as being obvious over Lu *et al.* (US2004/0191269) in view of Sanders *et al.* (2002).

The instant invention is further limited to a mutation I559P in gp41 and a cleaved HIV-1 gp140. The disclosure of Lu *et al.* has been set forth above. Lu *et al.* do not disclose I559P substitution in gp41, however, Sanders *et al.* describe modifications of SOS gp140 that increase its trimer stability. A variant SOS gp140, designated SOSIP gp140, contains an isoleucine-to-proline substitution at position 559 in the N-terminal heptad repeat region of gp41. This protein is fully cleaved, has favorable antigenic properties, and is predominantly trimeric. See abstract.
It would have been obvious to one skilled in the art, at the time the invention was made, to modify the method of Lu *et al.* so that the protein boost contains a cleavage gp140 with I559P substitution inside the gp41 transmembrane region. One would be motivated to do so to increase the immunogenicity of the protein boost. There would be a reasonable expectation of success given that this protein has favorable antigenic properties, as suggested by Sanders *et al.*

Claims 40 and 42 lack an inventive step under PCT Article 33(3) as being obvious over Lu *et al.* (US2004/0191269) in view of Rickman *et al.* (1991).

The instant invention is further limited to administering a monophosphoryl lipd A (MPL) adjuvant in combination with the protein boost composition.
The disclosure of Lu *et al.* has been set forth above. Lu *et al.* do not disclose the MPL adjuvant, however, Rickman *et al.* describe the use of an adjuvant containing mycobacterial cell-wall skeleton, MPL, and squalene in a protein vaccine.
It would have been obvious to one skilled in the art, at the time the invention was made, to modify the method of Lu *et al.* by adding to the protein boost the adjuvant comprising the mycobacterial cell-wall skeleton, MPL, and squalene. One would be motivated to do

Supplemental Box
In case the space in any of the preceding boxes is not sufficient.

so to help stimulate immune response to the protein boost. There would be a reasonable expectation of success given that this adjuvant is superior to the standard adjuvant, aluminum hydroxide, as suggested by Rickman *et al.*

Claims 49-78, 82-92, and 102 lack an inventive step under PCT Article 33(3) as being obvious over Lu *et al.* (US2004/0191269) in view of Binley *et al.* (2000), Binley *et al.*(2002), Sanders *et al.*(2002), Rickman *et al.*(1991),and further in view of Josephson *et al.* (1999).

The instant invention is further limited to affixing the protein boost to a superparamagnetic particle.
The disclosure of Lu *et al.*, Sanders *et al.*, and Binley *et al.* (both '00 and '02) are set forth above. None of the references explicitly discloses a superparamagnetic particle, although Lu *et al.* clearly suggest that the kit can further contain a diagnostic or therapeutic agent to monitor a response to immune response to the compositions in hte subject. See ¶88 on page 8.
Josephson *et al.* disclose a biocompatible, dextran coated superparamagnetic iron oxide particle derivatized with a HIV Tat peptide for the purpose of intracellular magnetic labelling of different target cells. Labeled cells were highly magnetic, were detectable by NMR imaging, and could be retained on magnetic separation columns. The described method has potential applications for in vivo tracking of magnetically labeled cells by MR imaging and for recovering intracellularly labeled cells from organs. See abstract.
It would be obvious to one skilled in the art, at the time the invention was made, to modify the method of Lu *et al.* so that the protein boost is affixed to a superparamagnetic iron oxide particle for the purpose of labeling targets cells that bind to the injected immunogen, HIV gp140 or gp120-gp41 trimeric complex. One would be motivated to do so to detect any immune response to the injected immunogen. There would be a reasonable expectation of success given that HIV Tat affixed to the superparamagnetic beads were detectable and isolatable, as suggested by Josephson *et al.*

Claims 30, 41, 44-48, 79, 93-97, 99-101, and 103-105 meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest a method for preventing, reducing the likelihood of, or delaying the onset of, or slowing the rate of progression of HIV-1 infection.

Claims 1-30, 33-79 and 82-105 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry.